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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/572,794	03/21/2006	Bernard Christophe Barlaam	056291-5245	4231

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
12/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,794	BARLAAM ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,16,17,23-34 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,16,17,23-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/9/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I in the reply filed on 10-9-09 is acknowledged. The traversal is on the ground(s) that Group I seems to restrict out the optional substituents on Q^2 in claims 23-25. Thus, applicant has requested to include claims 23-25 in Group I since Q^2 has been amended to elected ring. The request has been found reasonable and is granted. Therefore, Group I is now revised as below:

Group 1: Claim(s) 1-19 and 23-37 (in part), drawn to compounds of formula I wherein:

Q^1 is piperidinyl ring;
Q^2 is isoxazolyl ring;

and pharmaceutical composition thereof, processes of making said compounds, and a method for producing an anti-proliferative effect using said compounds.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-15, 18-22, 35 and 36 are cancelled.

Claims 1-13, 16, 17, 23-34 and 37 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-13, 16, 17, 23-34 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 1 recites a proviso excluding the compound of formula I wherein Q^1 is a *morpholino*, which is not the same as *piperidinyl* ring as currently defined and elected for Q^1. Thus, said proviso is inconsistent with the definition of Q^1, and renders the claim indefinite.

b. Claim 31 lacks antecedent basis because it depends on claim 1 but recites a species that is outside the scope of claim 1. In particular, it is compound (11) which has Q^2 as a *pyrazolyl* ring, and not an *isoxazolyl* ring.

c. Claim 32, in several places, recites the phrase "except that" which suggests a proviso, but the statement following said phrase is not a proviso, instead it is a limitation. Thus, the phrase "except that" creates ambiguity.

d. Claim 37 recites the limitation of "anti-proliferative effect" which does not seem to have a definition. It is unclear what diseases are encompassed by said term besides benign and malignant tumours. The term could reads on a process hindering embryogenesis, in which case, it would be contradicting to the intended therapeutic effect.

e. Dependent claims which fail to remedy the deficiencies and problems expressed herein regarding independent claims under 35 USC 112 2nd Paragraph are rejected as containing said deficiencies and problems as the claims from which they depend.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claim 37 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of solid tumours such as: breast, colorectal, and naso-pharangeal, does not reasonably provide enablement for the treatment of other tumours or cancers that are encompassed by the term "anti-proliferative effect" which is alledgedly related to erbB. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;
(2) The amount of direction or guidance presented;
(3) The state of the prior art;
(4) The relative skill of those in the art;
(5) The predictability or unpredictability of the art;
(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 37 recites a "method for producing an anti-proliferative effect..." The term "proliferative effect" covers all types of tumors, cancers as well as other diseases. Examples of various tumors and cancers include Lymphoblastic Leukemia, Myeloid Leukemia, Adrenocortical Carcinoma, Hepatocellular Cancer, Liver Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Soft Tissue Sarcoma, AIDS-related Maglinancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Tumors, Breast Cancer, CNS Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Medulloblastoma, Pancreatic Cancer, Endometrial Cancer, Ewing's Sarcoma, Gastric Cancer, Germ Cell Tumors, Gestational Trophoblastic Tumors, Hairy Cell Leukemia, Head and Neck Cancer, Intraocular Melonoma, Hypopharyngeal Cancer, Intestinal Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lung Cancer, Osteosarcoma, Skin Cancer, Retinoblastoma, Rhabdomyosarcoma, Thyoma,... etc. It also covers all growing processes like angiogenesis, embryogenesis, hair growth, bone development, hemogenesis, etc.

Thus, the scope of claim 37 is unduly broad because by recting "anti-proliferative effect", all processes of growth are affected be it cancerous or not.

The amount of direction or guidance presented: The claimed compound inhibits epidermal growth factor receptor (EGFR), erbB2, HER3 or HER4. Said receptors are found in cancers such as: breast, ovarian, colorectal, prostate and lung cancer. The specification does not provide data or evidence on reduction of tumor size or cell growth for other cancers that are not related to the cited receptors.

The state of the prior art: A commercially known compound, Iressa or Gefitinib which, in a preclinical studies, is shown to treat cancers such as: prostate, ovarian, breast, colon, small-cell and non-small-cell lung, and ductal carcinoma. Even for the listed cancers, "only tumors in which inhibition of the receptor results in inhibition of down stream signaling pathways are growth arrested." (see page 861 (right column), **Grünwald V. et. al.**, REVIEW, J. Nat. Can. Inst., Vol. 95, No. 12, 6/18/03). Thus, the state of the art does not correlate the inhibition of EGFR to all types of cancers as encompassed by the term "proliferative effect". Therefore, the state of the art does not support the scope of the claimed method.

The relative skill of those in the art: There has never been a compound capable of treating cancer generally, let alone treating all kinds of diseases related to EGFR which can affect normal growth. Different types of cancers affect different organs and have different modes of growth and harm to the body as well as different vulnerabilities. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Therefore, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or all proliferative disorders in general.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the showing of EGFR inhibition alone does not guarantee the compound's effectiveness in treating cancers that are not related to EGFR. With only three cell lines are tested, namely, LoVo (colorectal adenocarcinoma), MCF-7 (breast carcinoma), KB (naso-

pharangeal carcinoma), there is no sufficient data to support a wide range of tumours and cancers that affect different organs (cell types), and manifestation.

With specific reference to cancer, *Ex parte Kranz*, 19 USPQ2d 1216, 1219 notes the "general unpredictability of the field [of] ...anti-cancer treatment." *In re Application of Hozumi et al.*, 226 USPQ 353 notes the "fact that the art of cancer chemotherapy is highly unpredictable". More generally, the invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, given the unpredictable nature of the art, and the preliminary research in the art, one skilled in the art will have to carry out undue experimentation to practice the method of treatment recited in claim 37. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, ***In re Ferens***, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal requires undue experimentation, ***Genetech vs. Novo Nordisk***, 42 USPQ 2nd 1001, 1006.

Information Disclosure Statement

3. The IDS of 3/21/06, 9/13/06, 4/20/07, 1/28/08 and 10/9/09 have been considered. All cited foreign documents need to have names. Applicant is suggested to provide a completely filled form 1449 (i.e., document number, name, date, etc.).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

12-17-09